REMARKS

Claims 5, 8 to 16, 18, 20 to 24, 27 to 31, and 54 to 55, as amended, are present.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Claims 5, 9 and 27 have been amended to specifically define the enteric coating polymer employed as set out in Claims 9 and 10 thereby specifically excluding hydroxypropylmethyl cellulose phthalate from the enteric coating.

The following remarks relate to the Final Official Action mailed August 23, 2005.

Claims 5, 8 to 24, 27 to 31, 54 and 55 are rejected under 35 U.S.C. §112, first paragraph. The Examiner maintains that "applicants' specification does not provide support for the limitation said enteric coating excluding hydroxypropylmethyl cellulose phthalate" in claims 5 and 27.

The claims as now present and amended do not include the above objected to limitation.

A discussion of Applicants' invention as claimed follows.

The ddI (HIV inhibitor-antiviral) formulations of the prior art are chewable/dispersible buffered tablets which must be thoroughly chewed, or manually crushed or uniformly dispersed in water prior to administration. Moreover, as ddI is highly acid labile, the prior art formulations, including the chewable/dispersible form and the powder formulation for oral solution, contain buffering agents. In the pediatric form, ddI must be administered in combination with antacids. The buffers and antacids frequently lead to significant gastrointestinal imbalance as noted by sever diarrhea which may in turn impede drug absorption.

Patients have also complained about chewing the very large ddI tablets as well as the unpleasant taste of ddI and the bitter and chalky taste of buffers. This also applies to the oral solutions of ddI which must be dispersed in a large volume of water, which, moreover, is very time consuming.

All of the above factors impede the patients regular intake of the drug. Thus, there has been a great need for a ddI formulation which is simple to use and without the aforementioned problems and thus readily acceptable to the patient.

In spite of the fact that the antiviral agent ddI has been available for a very long time, it was not until the present invention that a formulation was developed which is readily acceptable to the patient.

As set out in the claims as amended the problems associated with the prior art ddI formulations are avoided by formulating the active ingredient ddI at a surprisingly high drug load (80 to 100%) in enteric-coated beadlets. The enteric coating of the beadlets as now defined in the claims specifically includes polyvinylacetate phthalate, cellulose acetate phthalate, or a methacrylic acid copolymer and does not include hydroxypropylmethyl cellulose phthalate. In addition, use of the enteric coating enables the enteric-coated beadlets to be devoid of a protective subcoat between the core and the enteric coating of the beadlet.

More specifically, Applicants' invention as claimed is defined as a pharmaceutical composition (Claim 5) which includes a core in the form of a beadlet which contains from about 80 to about 100% by weight of an acid labile medicament which is 2',3'-dideoxyinosine (ddI), and which core may also include a disintegrant and/or a binder, and an enteric coating for the core. Applicants specifically exclude the presence of a protective coat or subcoat between the core and the enteric coating since the enteric coating will not attack the ddI in the core and the ddI in the core will not attack or cause the enteric coating to dissolve or otherwise disintegrate prematurely. The enteric coating in Applicants' beadlets will dissolve at the desired time, that is, when it is subjected to a pH of 4.5 or higher. As indicated in the Specification at page 7 starting on line 18, the enteric coating will permit drug release at a pH of 4.5 or higher (such as found in the upper intestines) and should not dissolve before it reaches the duodenum.

In light of the multitude of possible excipients, carriers, coatings as well as dosage forms available, the person of skill in the art could not have arrived at the instant solution by a mere consideration of the prior art, particularly taking into account the special physicochemical properties of ddI as well as its pharmacodynamic profile.

Claims 5, 8 to 24, 27 to 31, 54 and 55 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hodges et al. (US 5,225,202), in view of Tanaka et al. (US 5,109,003).

The Examiner contends that

> "Hodges teaches coated pellets composition comprising drug-containing core, and an enteric coating layer surrounding the core, wherein the enteric coating will provide protection of the medicament at pH less than 3, but will allow for drug release at a pH of 4.5 or higher (see abstract; column 2, lines 35-53; and column 3, lines 10-15). Drug in the core is an acid labile drug includes dideoxyinosine (ddI) (column 3, lines 16-19). The core further comprising one or more disintegrants such as sodium starch glycolate, corn starch, or cross-linked polyvinylpyrrolidone in an amount of from about 2 to about 15%; and binder in an amount of from 0 to about 20%

(column 3, lines 20-26, 54-64). The enteric coating layer comprising hydroxypropylmethyl cellulose phthalate (HPMCP); plasticizer such as diethyl phthalate, triethyl citrate, or polyethylene glycol; and anti-adherent such as talc, magnesium stearate, or fumed silica (column 4, lines 17-51). The coated pellets may be filled into hard shell capsule (column 6, lines 3-4). Hodges further teaches the use of buffering agent in the core, as well as in the enteric coating layer, such as sodium hydroxide (see abstract, column 3, lines 5-10, and column 4, lines 38-39). Hodges also teaches the subcoat layer between the core and outer enteric coating layer. However, Hodges discloses that the subcoat layer *may* be needed only where the core includes a drug which is incompatible with the enteric coating layer (column 4, lines 59-65). It is noted that all of Hodges' examples that include the subcoat layer show the use of pravastatin as the active agent. None of the examples show subcoat layer used in ddI composition.

Hodges does not explicitly teach the amounts of the ingredients, as well as sodium carboxymethylcellulose as a binder, and methacrylic acid being the enteric coating polymer. However, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Regarding sodium carboxymethylcellulose, and methacrylic acid copolymers, it is the position of the examiner that sodium carboxymethylcellulose is a well known binder, and methacrylic acid copolymer is a well known enteric coating polymer. However, to be more specific, Tanaka is cited, wherein Tanaka teaches an enteric coating composition comprising binder such as sodium carboxymethylcellulose, and enteric coating polymer includes HPMCP or methacrylic acid copolymers (column 5, lines 46-64). Thus, it would have been obvious for one of ordinary skill in the art to modify the coated pellets composition of Hodges using sodium carboxymethylcellulose as the binder, and methacrylic acid copolymers as the enteric coating polymer in view of the teaching of Tanaka, because Tanaka teaches an enteric coating composition comprising a well known binder and a well known enteric coating polymer such as HPMCP and methacrylic acid copolymers, and because Hodges teaches an enteric coated pellets composition that has good resistance to deterioration at pH less than 3 but have good drug release properties at greater than 3."

The Examiner further maintains that,

"Moreover, Takada et al., the secondary reference, teaches an enteric coating includes hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, polyvinyl alcohol phthalate, methyl methacrylate, methacrylic acid copolymer, and methyl acrylatemethacrylic acid copolymer (column 5, lines 58-66). Thus, it would have been obvious for one of ordinary skill in the art to modify the enteric coating of Hodges using methyl methacrylate, methacrylic acid copolymer, and methyl acrylatemethacrylic acid copolymer, because Takada recognizes the equivalency of the enteric coating polymer including hydroxypropylmethyl cellulose and the methacrylic acid copolymer."

It is submitted that Applicants' beadlet formulation as claimed in Claims 5, 8 to 24, 27 to 31, 54 and 55 is patentable over Hodges et al. taken with Tanaka et al.

U.S. Patent No. 5,225,202 to Hodges et al. discloses a pharmaceutical composition which includes a core containing

(1) a medicament which is sensitive to a low pH environment, such as pravastatin or 2',3'-dideoxyinosine; Hodges et al. discloses that pravastation will be present in an amount from about 1 to about 60% by weight of the composition (column 3, lines 13 to 15). There is no disclosure in Hodges et al. of the concentration of ddI which would be employed or any formulation containing ddI;

(2) a buffering agent to raise pH to ensure rapid drug release between pH's 4 and 5 and to aid in minimizing drug degradation in the core due to acid ingress in low pH environments (Col. 3, lines 6 to 9); and

(3) an enteric coating, which includes a neutralized form of hydroxypropylmethyl cellulose phthalate, and a plasticizer.

In Col. 4, starting at line 59, Hodges et al. states that

> "where the core includes a drug which is incompatible with the enteric coating layer, a subcoat layer which acts as a physical barrier between the core and outer enteric coating layer will be employed."

Since the drug ddI is incompatible with the enteric coating layer, Hodges et al. will have to employ a subcoat layer. It is not optional under these circumstances. The only formulations disclosed in Hodges et al. contain pravastatin and a subcoat is always present. Hodges et al. does not disclose formulations containing ddI. The subcoat is employed in the pravastatin formulations even though the Hodges et al. core includes a buffer (sodium citrate) and the enteric coat includes a buffer (sodium hydroxide). Thus, even with the use of buffers, because of the nature of the enteric (HPMCP), Hodges et al. still must use a subcoat. It therefore must be assumed that Hodges et al. would have to employ a subcoat with ddI since the enteric coat must include HPMCP.

Hodges et al. will include a binder in the core which, as disclosed in Col. 3, lines 58 to 65, is polyvinylpyrrolidone, lactose, starches such as corn starch, modified corn starch,

sugars, gum acacia, or a wax binder such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

It is submitted that Applicants' pharmaceutical composition as now claimed is patentable over Hodges et al. for the following reasons:

(1) Applicants' beadlet contains 80 to 100% ddI. Hodges et al. only discloses use of 1 to 60% pravastatin. There is no disclosure of how much ddI should be included.

(2) Applicants do not include a subcoat layer as would be required by Hodges et al. where the drug is 2′,3′-dideoxyinosine since in Applicants' composition there is no incompatibility between the 2′,3′-dideoxyinosine and the enteric coating.

(3) Applicants use an enteric coating which does not include hydroxypropylmethyl cellulose phthalate which is required in Hodges et al.

In view of the above differences, which differs are unobvious, it is submitted the Applicants' composition as claimed is patentable over Hodges et al.

U.S. Patent No. 5,109,003 to Tanaka et al. discloses enteric-coated tablets or granules containing a peptic ulcer drug, which enteric coating may include HPMCP or a methacrylic acid copolymer. The peptic ulcer drug has nothing whatsoever to do with ddI.

Applicants' invention as claimed is directed to enteric-coated beadlets and not an enteric-coated tablet or granule as disclosed by Tanaka et al. taken above.

Applicants' enteric coated beadlets include 2′,3′-dideoxyinosine and not an ulcer drug as in Tanaka et al. Applicants' beadlets contain 80 to 100% ddI. Tanaka et al. does not disclose or suggest how to make a beadlet (or any other type formulation) containing 80 to 100% drug.

Thus, it is seen that the very nature and inventive concept of Tanaka et al. is totally different from Applicants' composition as claimed. It is therefore submitted that Applicants' composition as claimed is patentable over Tanaka et al. taken above.

Applicants' composition as claimed is clearly patentable over a combination of Hodges et al. and Tanaka et al.

Neither of the cited references taken singly or in combination discloses or suggests or gives the slightest hint of a spheronized beadlet or any other dosage form which contains 80 to 100% by weight of ddI or how to go about making such a spheronized beadlet containing at least 80% ddI.

ddI is a very acid labile (which degrades in the stomach when contacted with gastric acid) and requires large amounts of buffers or antacids which could lead to significant GI problems. In addition, use of large amounts of buffers with ddI requires large ddI tablets (a single dose is two tablets of 2.1 g each).

These problems are alleviated according to Applicants' invention by preparing smaller dosage forms as described below, for example, beadlets containing high concentrations of ddI, which beadlets will include an enteric coating.

Until now, it has not been possible to formulate solid oral dosage forms containing large amounts of ddI (at least 80% by weight) without using large amounts of buffers or highly water soluble salt forms of ddI. Applicants' are able to prepare beadlets containing at least 80% ddI by dusting the extrudate and the forming beadlet with the ddI.

There is no disclosure or suggestion in either of the cited references each taken singly or in combination of forming beadlets containing at least 80% by weight 2',3'-dideoxyinosine or at least 80% by weight 2',3'-ddeoxyinosine in the core. This is not easily accomplished and it is through use of a unique 2',3'-dideoxyinosine dusting step that such high concentrations are achievable as described on page 12 of the Specification and in the working examples. As indicated on page 12, by dividing a dry blend of 2',3'-dideoxyinosine, binder and disintegrant into two portions, one portion of which is made into beadlets using a spheronizer, and the other portion of which is dusted onto the beadlets during spheronization, Applicants are able to make their beadlets having the desired high concentration of 2',3'-dideoxyinosine. The cited references are completely devoid of a teaching or suggestion as to how to make the enteric coated beadlets of the invention which contain at least 80% by weight ddI.

The present situation with regard to lack of teaching in cited references of how to make the ddI beadlet formulation containing at least 80% by weight ddI is not unlike where the cited prior art names a compound but where no known or obvious method exists for making that compound and thus the cited prior art will not place the compound in the possession of the public. In re Hoeksena, 158 U.S.P.Q. 596 (CCPA 1968). A compound is not obvious if there is no known way or obvious way to prepare it. In re Hoeksema et al., supra. By the same token, a formulation is not obvious if there is no known way to prepare it. It is Applicants' contention that the cited prior art taken alone or in any combination does not disclose or suggest Applicants' enteric coated beadlet formulation as claimed or a method for preparing same or a method for preparing the Hodges et al. formulation if it contained at least 80% by weight ddI, which it does not (Hodges contains only up to 60%

drug), or a method for preparing the Tanaka et al. formulation if it contained at least 80% by weight ddI. Therefore, Hodges and Tanaka do not place Applicants' formulatin in the public.

The Examiner has not established a prima facie case of obviousness. The cited references taken in combination do not disclose or suggest a formulation containing at least 80% ddI. That this is apparent can be seen from the fact that neither of the cited references even discloses a formulation containing ddI. In addition, the cited references taken in combination do not teach how to make a ddI formulation containing at least 80% ddI. In determining patentability of a composition, it is appropriate to consider the manner of its preparation versus the prior art; if there is no disclosure of how to make it, it cannot be considered in the possession of the public. In re Hoeksema et al., supra. There is no disclosure in the cited art taken in combination of how to make a formulation containing at least 80% ddI as explained hereinbefore.

In view of the above, it is clear that the Examiner has not cited any references each taken alone or in combination which would make Applicants' formulation obvious.

It is also submitted that the very combination of Hodges et al. taken in view of Tanaka et al. is improper as lacking any foundation and could only be made with the use of hindsight in view of Applicants' disclosure. The cited prior art does not provide a suggestion or basis for modifying Hodges et al. and Tanaka et al.

Hodges et al. requires an enteric coating which includes hydroxypropylmethyl cellulose phthalate and a protective subcoat, both of which are excluded from Applicants' beadlets as claimed.

Tanaka et al. does not relate to beadlets. The technology of enteric-coated tablets or granules is different from beadlets. In fact, absent the use of hindsight in view of Applicants' disclosure, one skilled in the art would have no reason to combine the teachings of Hodges et al. and Tanaka et al. Therefore, the combination of these references is improper and should be withdrawn. Regardless, the above combination of references does not make Applicants' beadlets as claimed obvious since neither of the cited references alone or in combination teaches or discloses how to make a composition containing ddI let alone enteric coated beadlets containing at least 80% ddI.

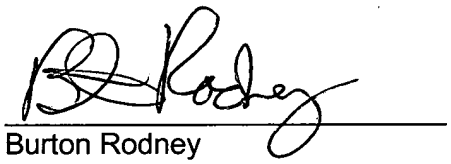
Applicants are not claiming a process or a product by process herein. However, the fact that the cited references do not disclose or suggest a procedure for preparing beadlets or pellets of high concentration of 2',3'-dideoxyinosine as claimed further support

Applicants' case for patentability of their beadlet containing at least 80% by weight 2',3'-dideoxyinosine.

It is submitted that there is no disclosure or suggestion in either of the cited references or combination thereof of the claimed composition. Accordingly, absent the use of hindsight in view of Applicants' disclosure, there would be no reason for one skilled in the art reading the cited references to combine these references. The use of hindsight in view of Applicants' disclosure in combining references to reject Applicants' claims is clearly improper in view of In re Pye et al., 148 U.S.P.Q. 426 (CCPA 1966).

In view of the foregoing, it is believed that Claims 5, 8 to 16, 20 to 24, 27 to 31, and 54 and 55 are in condition for allowance.

Respectfully submitted,



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Date: November 22, 2005